=> fil reg

FILE 'REGISTRY' ENTERED AT 16:21:44 ON 27 MAR 2000
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

STRUCTURE FILE UPDATES: 26 MAR 2000 HIGHEST RN 260044-18-6
DICTIONARY FILE UPDATES: 26 MAR 2000 HIGHEST RN 260044-18-6

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 13, 1999

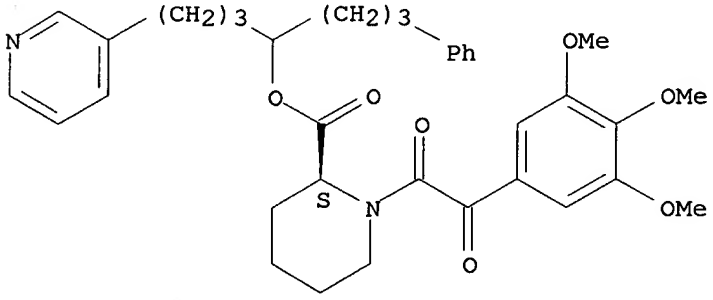
Please note that search-term pricing does apply when conducting SmartSELECT searches.

Structure search limits have been increased. See HELP SLIMIT for details.

=> d ide can tot l2

L2 ANSWER 1 OF 4 REGISTRY COPYRIGHT 2000 ACS
RN 188614-94-0 REGISTRY
CN 2-Piperidinecarboxylic acid, 1-[oxo(3,4,5-trimethoxyphenyl)acetyl]-, 1-(3-phenylpropyl)-4-(3-pyridinyl)butyl ester, (2S)- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN V 10367
FS STEREOSEARCH
MF **C35 H42 N2 O7**
SR CA
LC STN Files: CA, CAPLUS, DRUGNL, DRUGUPDATES, TOXLIT, USPATFULL

Absolute stereochemistry.



9 REFERENCES IN FILE CA (1967 TO DATE)
9 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 130:346620

REFERENCE 2: 130:47360

REFERENCE 3: 128:252907

REFERENCE 4: 128:205136

REFERENCE 5: 128:30302

REFERENCE 6: 127:44315

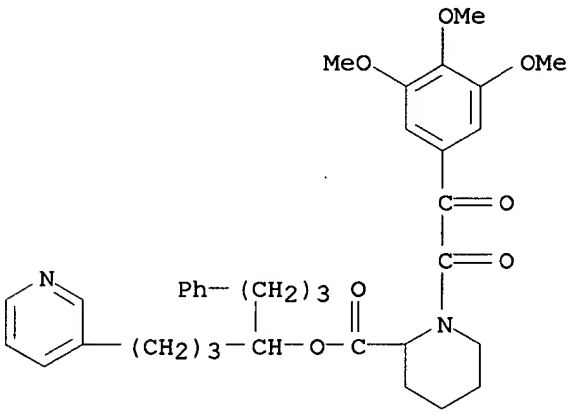
REFERENCE 7: 127:13470

REFERENCE 8: 126:343875

Point of Contact:
Jan Delaval
Librarian-Physical Sciences
CM1 1E01 Tel: 308-4498

REFERENCE 9: 126:272378

L2 ANSWER 2 OF 4 REGISTRY COPYRIGHT 2000 ACS
RN 145913-08-2 REGISTRY
CN 2-Piperidinecarboxylic acid, 1-[oxo(3,4,5-trimethoxyphenyl)acetyl]-, 1-(3-phenylpropyl)-4-(3-pyridinyl)butyl ester (9CI) (CA INDEX NAME)
MF **C35 H42 N2 O7**
SR CA
LC STN Files: CA, CAPLUS, TOXLIT



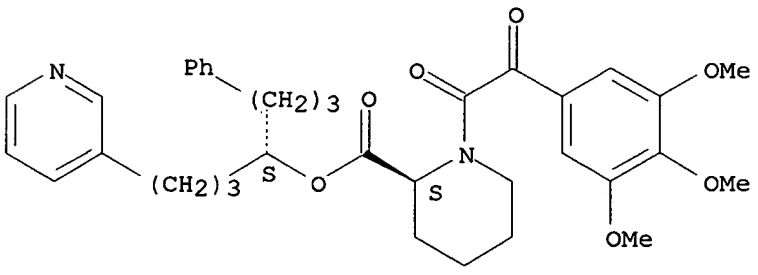
2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 123:217939

REFERENCE 2: 119:95338

L2 ANSWER 3 OF 4 REGISTRY COPYRIGHT 2000 ACS
RN 145913-00-4 REGISTRY
CN 2-Piperidinecarboxylic acid, 1-[oxo(3,4,5-trimethoxyphenyl)acetyl]-, 1-(3-phenylpropyl)-4-(3-pyridinyl)butyl ester, [S-(R*,R*)]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF **C35 H42 N2 O7**
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.



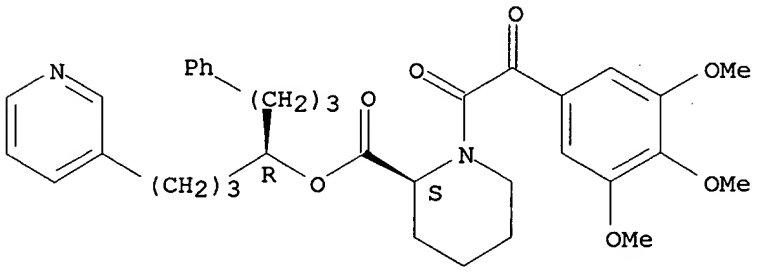
2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 122:55896

REFERENCE 2: 119:95338

L2 ANSWER 4 OF 4 REGISTRY COPYRIGHT 2000 ACS
RN 145912-99-8 REGISTRY
CN 2-Piperidinecarboxylic acid, 1-[oxo(3,4,5-trimethoxyphenyl)acetyl]-, 1-(3-phenylpropyl)-4-(3-pyridinyl)butyl ester, [R-(R*,S*)]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF **C35 H42 N2 O7**
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.



2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 122:55896

REFERENCE 2: 119:95338

=> d his l2-

(FILE 'REGISTRY' ENTERED AT 16:17:07 ON 27 MAR 2000)
L2 4 S L1 NOT 2 PYRIDINYL
SEL RN
L3 0 S E1-E4/CRN

FILE 'HCAOLD' ENTERED AT 16:19:02 ON 27 MAR 2000
L4 0 S L2

FILE 'HCAPLUS' ENTERED AT 16:19:09 ON 27 MAR 2000
L5 12 S L2
L6 4 S V10367 OR V()(10367 OR 10 367)
L7 13 S L5,L6
E GOLD B/AU
L8 47 S E3,E5,E35,E36
L9 2 S L7 AND L8
L10 13 S L7,L9

FILE 'USPATFULL' ENTERED AT 16:20:38 ON 27 MAR 2000
L11 4 S L2
L12 1 S V10367 OR V()(10367 OR 10 367)
L13 5 S L11,L12
E GOLD B/AU
L14 1 S E16
L15 1 S L13 AND L14
L16 5 S L13,L15

FILE 'HCAPLUS, USPATFULL' ENTERED AT 16:21:34 ON 27 MAR 2000
L17 16 DUP REM L10 L16 (2 DUPLICATES REMOVED)

FILE 'REGISTRY' ENTERED AT 16:21:44 ON 27 MAR 2000

=> fil hcaplus uspatful

FILE 'HCAPLUS' ENTERED AT 16:22:03 ON 27 MAR 2000
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FILE 'USPATFULL' ENTERED AT 16:22:03 ON 27 MAR 2000
CA INDEXING COPYRIGHT (C) 2000 AMERICAN CHEMICAL SOCIETY (ACS)

=> d l17 bib abs hitrn tot

L17 ANSWER 1 OF 16 USPATFULL
AN 2000:31444 USPATFULL
TI Methods and compositions for stimulating neurite growth
IN Armistead, David M., Maynard, MA, United States
PA Vertex Pharmaceuticals Incorporated, Cambridge, MA, United States (U.S. corporation)
PI US 6037370 20000314
AI US 1995-486004 19950608 (8)
DT Utility
EXNAM Primary Examiner: Criares, Theodore J.
LREP Fish & Neave; Haley, Jr., James F.; Marks, Andrew S.
CLMN Number of Claims: 11
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1325
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to methods and pharmaceutical compositions for stimulating the growth of neurites in nerve cells. The compositions comprise a neurotrophic amount of a compound which binds to the FK-506 binding protein (FKBP) and a neurotrophic factor, such as nerve growth factor NGF. The methods comprise treating nerve cells with the above-described compositions or compositions comprising the FKBP binding compound without a neurotrophic factor. The methods of this invention can be used to promote repair of neuronal damage caused by disease or physical trauma.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **188614-94-0**
(compds. with affinity for FKBP12 in combination with neurotrophic factors for stimulating neurite growth)

L17 ANSWER 2 OF 16 USPATFULL
AN 1999:128537 USPATFULL
TI Compositions and methods for promoting nerve regeneration
IN **Gold, Bruce G.**, West Linn, OR, United States
PA Orgegon Health Sciences University, Portland, OR, United States (U.S. corporation)
PI US 5968921 19991019
AI US 1997-956691 19971024 (8)
DT Utility
EXNAM Primary Examiner: Weddington, Kevin E.
LREP Klarquist Sparkman Campbell Leigh & Whinston, LLP
CLMN Number of Claims: 36
ECL Exemplary Claim: 1
DRWN 15 Drawing Figure(s); 7 Drawing Page(s)
LN.CNT 1254
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB FK506 and geldanamycin promote nerve regeneration by a common mechanism that involves the binding of these compounds to polypeptide components of steroid receptor complexes other than the steroid hormone binding portion of the complex (FKBP52 and hsp90, respectively). These and other agents cause hsp90 dissociation from steroid receptor complexes or block

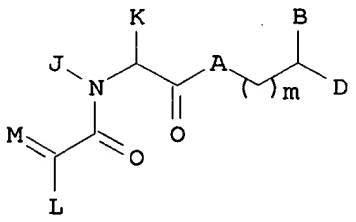
association of hsp90 with steroid receptor complexes.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

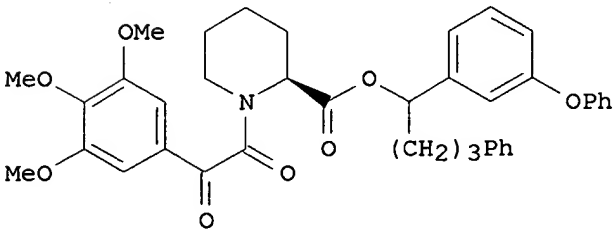
L17 ANSWER 3 OF 16 HCAPLUS COPYRIGHT 2000 ACS DUPLICATE 1
AN 1998:157415 HCAPLUS
DN 128:205136
TI Preparation of acylated amino acid derivatives for multi-drug resistance therapies and immune suppression.
IN Armistead, David M.; Harding, Matthew W.; Saunders, Jeffrey O.; Boger, Joshua S.
PA Vertex Pharmaceuticals Inc., USA
SO U.S., 34 pp. Cont.-in-part of U.S. 5,620,971.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 4

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5723459	A	19980303	US 1995-377315	19950124
US 5620971	A	19970415	US 1994-217982	19940325

PRAI US 1991-697785 19910509
US 1992-881152 19920511
US 1992-952299 19920928
US 1993-127814 19930928
US 1994-217982 19940325
OS MARPAT 128:205136
GI



I



III

AB The present invention relates to novel acylated amino acid esters I [A = CH2, O, NH, alkylimino; B, D = (un)substituted (hetero)aryl, alk(en)(yn)yl, cycloalk(en)ylalk(en)(yn)yl, (hetero)aralkyl, cis-C(Q):CHT; Q = H, alk(en)(yn)yl; T = (un)substituted (hetero)aryl, substituted cycloalkyl; L = H, U; M = O, CHU; U = H, alk(en)yl, cycloalk(en)ylalk(en)yl, (hetero)aralk(en)yl, (hetero)aryl; J = H, alkyl, CH2Ph; K = alkyl, CH2Ph, cyclohexylmethyl; or JK = atoms to form 5- to 7-membered, optionally O- or S-contg. heterocycle; m = 0-3; various provisos], as well as pharmaceutical compns. comprising them, which possess a broad range of useful biol. activities. These compds. can maintain, increase, or restore sensitivity of cells to therapeutic or prophylactic agents. They can also suppress, modify, or significantly reduce an immune response, including an autoimmune response in a mammal.

This invention also relates to pharmaceutical compns. comprising these compds. The compds. and pharmaceutical compns. of this invention are particularly well-suited for treatment of multi-drug resistant cells, for prevention of the development of multi-drug resistance, for use in multi-drug resistant cancer therapy, and for prevention or treatment of graft rejection and various autoimmune diseases. Over 100 I are reported, including both single and mixed diastereomers. Thus, 3-PhOC6H4CH2OH underwent oxidn. to the aldehyde and reaction with Ph(CH2)3MgBr to give the racemic alc. 3-PhOC6H4CH(OH)(CH2)3Ph (II). Esterification of II with (S)-N-[(3,4,5-trimethoxyphenyl)glyoxyl]pipecolic acid (prepn. given) yielded ester III as a mixt. of diastereomers. In a test for reversal of multi-drug-resistance by a line of L1210 cells, selected I gave up to 18-fold increase in the antiproliferative potency of doxorubicin.

IT **188614-94-0P**
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of acylated amino acid esters for multi-drug resistance therapies and immune suppression.)

L17 ANSWER 4 OF 16 HCAPLUS COPYRIGHT 2000 ACS
AN 1999:66625 HCAPLUS
DN 130:306436
TI Tacrolimus (FK506) increases neuronal expression of GAP-43 and improves functional recovery after spinal cord injury in rats
AU Madsen, Joseph R.; MacDonald, Paul; Irwin, Nina; Goldberg, David E.; Yao, Gui-Lan; Meiri, Karina F.; Rimm, Ilonna J.; Stieg, Philip E.; Benowitz, Larry I.
CS Department of Neurosurgery, Children's Hospital, Boston, MA, 02115, USA
SO Exp. Neurol. (1998), 154(2), 673-683
CODEN: EXNEAC; ISSN: 0014-4886
PB Academic Press
DT Journal
LA English
AB Tacrolimus (FK506), a widely used immunosuppressant drug, has neurite-promoting activity in cultured PC12 cells and peripheral neurons. The present study investigated whether tacrolimus affects the expression of the neuronal growth-assocd. protein, GAP-43, as well as functional recovery after photothrombotic spinal cord injury in the rat. In injured animals receiving tacrolimus, the no. of neurons expressing GAP-43 mRNA and protein approx. doubled compared to that in injured animals receiving vehicle alone. This increase in GAP-43-pos. cells was paralleled by a significant improvement in neurol. function evaluated by open-field and inclined plane tests. Another FKBP-12 ligand (**V-10, 367**) had similar effects on GAP-43 expression and functional outcome, indicating that the obsd. effects of tacrolimus do not involve inhibition of the phosphatase calcineurin. Thus, tacrolimus, a drug which is already approved for use in humans, as well as other FKBP-12 ligands which do not inhibit calcineurin, could potentially enhance functional outcome after CNS injury in humans. (c) 1998 Academic Press.

L17 ANSWER 5 OF 16 HCAPLUS COPYRIGHT 2000 ACS
AN 1998:167740 HCAPLUS
DN 128:252907
TI Oral administration of a non-immunosuppressant FKBP-12 ligand speeds nerve regeneration
AU **Gold, Bruce G.**; Zeleny-Pooley, Michelle; Chaturvedi, Pravin; Wang, Min-Sheng
CS Center for Research on Occupational and Environmental Toxicology (CROET)/L606,. Oregon Health Sciences University, Portland, OR, 97201-3098, USA
SO NeuroReport (1998), 9(3), 553-558
CODEN: NERPEZ; ISSN: 0959-4965
PB Rapid Science Ltd.
DT Journal
LA English

AB We recently showed that s.c. injections of a non-immunosuppressant FK506 binding protein-12 (FKBP-12) ligand (**V-10367**) accelerates nerve regeneration in the rat sciatic nerve crush model. Here we examd. the oral efficacy of this compd. for speeding nerve regeneration. Rats receiving **V-10367** (5, 15 or 50 mg/kg/day) by oral gavage all demonstrated an increase in nerve regeneration compared to vehicle-treated controls. Functional recovery was obsd. earliest and axonal calibers of regenerating axons in the soleus nerve were largest in the 15 mg/kg group, mean axonal areas being increased by 66% compared to controls. Orally active non-immunosuppressant FKBP-12 ligands may be useful for the treatment of human peripheral nerve disorders.

IT **188614-94-0, V 10367**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(oral administration of non-immunosuppressant FKBP-12 ligand **V-10367** speeds nerve regeneration)

L17 ANSWER 6 OF 16 HCAPLUS COPYRIGHT 2000 ACS
AN 1999:125753 HCAPLUS
DN 130:346620
TI Small molecule inducers of neurotrophic function
AU Wood, Paul L.
CS Neurex Corporation, Menlo Park, CA, 94025-1012, USA
SO IDrugs (1998), 1(4), 452-455
CODEN: IDRUFN; ISSN: 1369-7056
PB Current Drugs Ltd.
DT Journal; General Review
LA English
AB A review with 37 refs. on neurotrophic actions of immunophilin ligands, GPI-1046 and VA-10367, and compds., SR-57746A and AIT-082, that are currently in preclin. development but are devoid of immunosuppressant actions.
IT **188614-94-0**
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(small mol. inducers of neurotrophic function)

L17 ANSWER 7 OF 16 HCAPLUS COPYRIGHT 2000 ACS
AN 1998:633484 HCAPLUS
DN 130:47360
TI A novel immunophilin ligand: distinct branching effects on dopaminergic neurons in culture and neurotrophic actions after oral administration in an animal model of Parkinson's disease
AU Costantini, L. C.; Chaturvedi, P.; Armistead, D. M.; McCaffrey, P. G.; Deacon, T. W.; Isacson, O.
CS Neuroregeneration Laboratory, Program in Neuroscience, Harvard Medical School, Mclean Hospital, Belmont, MA, 02139, USA
SO Neurobiol. Dis. (1998), 5(2), 97-106
CODEN: NUDIEM; ISSN: 0969-9961
PB Academic Press
DT Journal
LA English
AB Protection or regeneration of the dopaminergic (DA) system would be of significant therapeutic value for Parkinson's disease. Immunophilin ligands, such as FK506, can produce neurotrophic effects in vitro and in vivo, but their immunosuppressive effects make them unsuitable for neurol. application. This study demonstrates that a novel, nonimmunosuppressive immunophilin ligand (**V-10,367**) increased the no. of neurites extended by tyrosine hydroxylase pos. (TH+) DA neurons in embryonic day 14 primary DA neuronal cultures. In contrast, the immunosuppressive immunophilin ligand FK506 increased the length of TH+ neurites. After oral administration in MPTP-treated mice, **V-10,367** completely protected against MPTP-induced loss of striatal TH+ axonal d., while FK506 did not. These expts. demonstrate

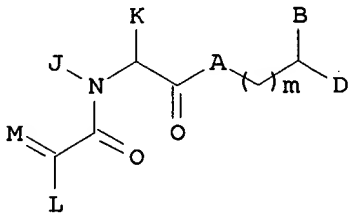
that nonimmunosuppressive immunophilin ligands specifically increase neurite branching in primary DA neuronal cultures and possess neurotrophic actions in vivo with potential application to neurodegenerative diseases. (c) 1998 Academic Press.

IT **188614-94-0, V-10367**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(immunophilin ligand: branching effects on dopaminergic neurons and neurotrophic actions after oral administration in a model of Parkinson's disease)

L17 ANSWER 8 OF 16 HCAPLUS COPYRIGHT 2000 ACS DUPLICATE 2
AN 1997:276774 HCAPLUS
DN 126:343875
TI Preparation of acylated amino acid derivatives for multi-drug resistance therapies and immune suppression.
IN Armistead, David M.; Saunders, Jeffrey O.; Boger, Joshua S.
PA Vertex Pharmaceuticals Incorporated, USA
SO U.S., 35 pp. Cont.-in-part of U.S. Ser. No. 881,152, abandoned.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 4

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5620971	A	19970415	US 1994-217982	19940325
	US 5723459	A	19980303	US 1995-377315	19950124

PRAI US 1991-697785 19910509
US 1992-881152 19920511
US 1992-952299 19920928
US 1993-127814 19930928
US 1994-217982 19940325
OS MARPAT 126:343875
GI



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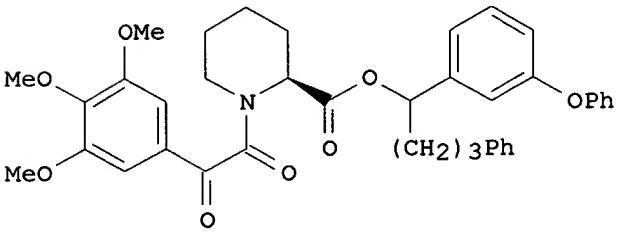


III

AB The present invention relates to novel acylated amino acid esters I [A = CH2, O, NH, alkylimino; B, D = (un)substituted (hetero)aryl, alk(en)(yn)yl, cycloalk(en)ylalk(en)(yn)yl, (hetero)aralkyl, cis-C(Q):CHT; Q = H, alk(en)(yn)yl; T = (un)substituted (hetero)aryl, substituted cycloalkyl; L = H, U; M = O, CHU; U = H, alk(en)yl, cycloalk(en)ylalk(en)yl, (hetero)aralk(en)yl, (hetero)aryl; J = H, alkyl,

CH2Ph; K = alkyl, CH2Ph, cyclohexylmethyl; or JK = atoms to form 5- to 7-membered, optionally O- or S-contg. heterocycle; m = 0-3; various provisos], as well as pharmaceutical compns. comprising them, which possess a broad range of useful biol. activities. These compds. can maintain, increase, or restore sensitivity of cells to therapeutic or prophylactic agents. They can also suppress, modify, or significantly reduce an immune response, including an autoimmune response in a mammal. This invention also relates to pharmaceutical compns. comprising these compds. The compds. and pharmaceutical compns. of this invention are particularly well-suited for treatment of multi-drug resistant cells, for prevention of the development of multi-drug resistance, for use in multi-drug resistant cancer therapy, and for prevention or treatment of graft rejection and various autoimmune diseases. Over 100 I are reported, including both single and mixed diastereomers. Thus, 3-PhOC6H4CH2OH underwent oxidn. to the aldehyde and reaction with Ph(CH2)3MgBr to give the racemic alc. 3-PhOC6H4CH(OH)(CH2)3Ph (II). Esterification of II with (S)-N-[(3,4,5-trimethoxyphenyl)glyoxyl]pipecolic acid (prepn. given) yielded ester III as a mixt. of diastereomers. In a test for reversal of multi-drug-resistance by a line of L1210 cells, selected I gave up to 18-fold increase in the antiproliferative potency of doxorubicin.

IT **188614-94-0P**
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of acylated amino acid esters for multi-drug resistance therapies and immune suppression.)

L17 ANSWER 9 OF 16 HCAPLUS COPYRIGHT 2000 ACS
AN 1997:397372 HCAPLUS
DN 127:13470
TI Neurotrophic pipecolic acid derivs. as rotamase inhibitors for treatment of neurodegenerative disorders
IN Steiner, Joseph P.; Hamilton, Gregory S.
PA Guilford Pharmaceuticals Inc., USA
SO PCT Int. Appl., 47 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9716190	A1	19970509	WO 1996-US13624	19960826
	W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN				
	US 5801197	A	19980901	US 1996-645149	19960513
	AU 9668573	A1	19970522	AU 1996-68573	19960826
	AU 713302	B2	19991125		
	EP 859614	A1	19980826	EP 1996-929014	19960826
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, FI				
	JP 11514643	T2	19991214	JP 1996-517308	19960826
	ZA 9608982	A	19980907	ZA 1996-8982	19961025
	NO 9801903	A	19980630	NO 1998-1903	19980427
PRAI	US 1995-551026	19951031			
	US 1996-645149	19960513			
	WO 1996-US13624	19960826			

OS MARPAT 127:13470
AB A method is disclosed of using specially formulated neurotrophic pipecolic acid derivs. (Markush included) having an affinity for FKBP-type immunophilins as inhibitors of rotamase enzyme activity to stimulate or promote neuronal growth or regeneration. The compds. of the invention may

be used in treatment of neurodegenerative disorders , e.g. Alzheimer's disease, Parkinson's disease, and other neuropathies.

IT **188614-94-0**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(neurotrophic pipecolic acid derivs. as rotamase inhibitors for treatment of neurodegenerative disorders)

L17 ANSWER 10 OF 16 USPATFULL
AN 97:68499 USPATFULL
TI Methods and compositions for stimulating neurite growth
IN Armistead, David M., Maynard, MA, United States
PA Vertex Pharmaceuticals Incorporated, Cambridge, MA, United States (U.S. corporation)
PI US 5654332 19970805
AI US 1995-486004 19950608 (8)
DT Utility
EXNAM Primary Examiner: Criares, Theodore J.
LREP Fish & Neave; Haley, Jr., James F.; Marks, Andrew S.
CLMN Number of Claims: 6
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1225
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to methods and pharmaceutical compositions for stimulating the growth of neurites in nerve cells. The compositions comprise a neurotrophic amount of a compound which binds to the FK-506 binding protein (FKBP) and a neurotrophic factor, such as nerve growth factor NGF. The methods comprise treating nerve cells with the above-described compositions or compositions comprising the FKBP binding compound without a neurotrophic factor. The methods of this invention can be used to promote repair of neuronal damage caused by disease or physical trauma.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **188614-94-0**
(compds. with affinity for FKBP12 in combination with neurotrophic factors for stimulating neurite growth)

L17 ANSWER 11 OF 16 HCAPLUS COPYRIGHT 2000 ACS
AN 1997:723133 HCAPLUS
DN 128:30302
TI A nonimmunosuppressant FKBP-12 ligand increases nerve regeneration
AU **Gold, Bruce G.**; Zeleny-Pooley, Michelle; Wang, Min-Sheng; Chaturvedi, Pravin; Armistead, David M.
CS Center for Research on Occupational and Environmental Toxicology, Oregon Health Sciences University, Portland, OR, 97201-3098, USA
SO Exp. Neurol. (1997), 147(2), 269-278
CODEN: EXNEAC; ISSN: 0014-4886
PB Academic
DT Journal
LA English
AB The immunosuppressant drugs FK506 and cyclosporin A inhibit T-cell proliferation via a common mechanism: calcineurin inhibition following binding to their resp. binding proteins, the peptidyl prolyl isomerases FKBP-12 and cyclophilin A. In contrast, FK506, but not cyclosporin A, accelerates nerve regeneration. In the present study, we show that the potent FKBP-12 inhibitor **V-10,367**, which lacks the structural components of FK506 required for calcineurin inhibition, increases neurite outgrowth in SH-SY5Y neuroblastoma cells and speeds nerve regeneration in the rat sciatic nerve crush model. In SH-SY5Y cells, **V-10,367** increased the lengths of neurite processes in a concn.-dependent (between 1 and 10 nM) fashion over time (up to 168 h). Daily s.c. injections of **V-10,367** accelerated the onset of clin. signs of functional recovery in the hind feet compared to vehicle-treated control

animals. Interdigit distances (between the first and fifth digits) measured on foot prints obtained during walking showed an increase in toe spread in **V-10,367**-treated rats compared to vehicle-treated controls. Electron microscopy demonstrated larger regenerating axons distal to the crush site in the sciatic nerve from **V-10,367**-treated rats. Quantitation of axonal areas in the soleus nerve revealed a shift to larger axonal calibers in **V-10,367**-treated rats (400 or 200 mg/kg/day); mean axonal areas were increased by 52 and 59%, resp., compared to vehicle-treated controls. FKBP-12 ligands lacking calcineurin inhibitory activity represent a new class of potential drugs for the treatment of human peripheral nerve disorders.

IT **188614-94-0, V 10367**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**V 10367**; nonimmunosuppressant FKBP-12 ligand **V-10,367** increases nerve regeneration)

L17 ANSWER 12 OF 16 HCAPLUS COPYRIGHT 2000 ACS
AN 1997:307496 HCAPLUS
DN 126:272378
TI Methods and compositions for stimulating neurite growth using compds. with affinity for FKBP12 in combination with neurotrophic factors
IN Armistead, David M.
PA Vertex Pharmaceuticals Incorporated, USA
SO S. African, 54 pp.
CODEN: SFXXAB
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	ZA 9604852	A	19960729	ZA 1996-4852	19960607
	US 6037370	A	20000314	US 1995-486004	19950608
	CA 2222430	AA	19961227	CA 1996-2222430	19960606
	WO 9641609	A2	19961227	WO 1996-US10123	19960606
	W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG				
	RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN				
	AU 9661119	A1	19970109	AU 1996-61119	19960606
	EP 831812	A2	19980401	EP 1996-918469	19960606
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	CN 1202104	A	19981216	CN 1996-195690	19960606
	BR 9609333	A	19991013	BR 1996-9333	19960606
PRAI	US 1995-486004	19950608			
	WO 1996-US10123	19960606			

OS MARPAT 126:272378

AB A pharmaceutically acceptable compn. is disclosed which comprises (a) a neurotropic amt. of a compd. with affinity for FK-506-binding protein FKBP12 e.g. having the formula BAC(:O)CH(K)N(J)C(:O)C(:E)D [A = O, NH, N(C1-4 alkyl); B = H, C1-6 (branched) alkyl, C2-6 (branched) alkenyl, C5-7 cycloalkyl, etc.; D = U; E = O, CHU (if D = H, then E = CH-U; if E = O, then D is not H); U = H, O-(C1-4)-straight or branched alkyl, O-(C2-4)-straight or branched alkenyl, C1-6 (branched) alkyl, C2-6 (branched) alkenyl, (substituted) C5-7 cycloalkyl, (substituted) C5-7 cycloalkenyl, etc.; J = H, C1-2 alkyl; K = C1-4 (branched) alkyl, benzyl, cyclohexylmethyl, or J and K taken together form 5-7 membered heterocyclic ring which may contain O, S, SO, SO2; and the stereochem. at carbon to which K is bonded = R or S] and pharmaceutically acceptable derivs. thereof; (b) a neurotrophic factor; and (c) a pharmaceutically carrier. The neurotrophic factor may be e.g. nerve growth factor. The methodol. of the invention can be used to promote repair of neuronal damage caused by

disease or phys. trauma.

IT **188614-94-0**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compds. with affinity for FKBP12 in combination with neurotrophic factors for stimulating neurite growth)

L17 ANSWER 13 OF 16 HCAPLUS COPYRIGHT 2000 ACS
AN 1997:415581 HCAPLUS
DN 127:44315
TI Structure based design of new therapeutic agents: biophysical analysis of FKBP12 complexed with immunosuppressants and de novo design of a novel FKBP12 ligand
AU Armistead, David M.; Harding, Matthew W.
CS Vertex Pharmaceuticals Incorporated, Cambridge, MA, USA
SO Princ. Drug Dev. Transplant. Autoimmun. (1996), 729-738. Editor(s): Lieberman, Ronald; Mukherjee, Asoke. Publisher: Landes, Austin, Tex. CODEN: 64NVAS
DT Conference; General Review
LA English
AB A review with 41 refs. on the biochem. role of immunophilins as principle drug targets, of the structure of FKBP12 and the FKBP12-FK506 complex, and of the de novo design of a first generation sub-nanomolar inhibitor of KKBP12 and initial biophys. details of the FKBP12-ligand structure.
IT **188614-94-0**
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(biophys. anal. of FKBP12 complexed with immunosuppressants and de novo design of novel FKBP12 ligand)

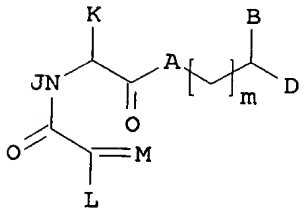
L17 ANSWER 14 OF 16 HCAPLUS COPYRIGHT 2000 ACS
AN 1995:749219 HCAPLUS
DN 123:217939
TI Design, synthesis and structure of non-macrocyclic inhibitors of FKBP12, the major binding protein for the immunosuppressant FK506
AU Armistead, D. M.; Badia, M. C.; Deininger, D. D.; Duffy, J. P.; Saunders, J. O.; Tung, R. D.; Thomson, J. A.; DeCenzo, M. T.; Futer, O.; et al.
CS Vertex Pharmaceuticals Incorporated, Cambridge, MA, 02139-4211, USA
SO Acta Crystallogr., Sect. D: Biol. Crystallogr. (1995), D51(4), 522-8 CODEN: ABCRE6; ISSN: 0907-4449
DT Journal
LA English
AB The authors have synthesized a series of non-macrocyclic ligands to FKBP12 that are comparable in binding potency and peptidyl prolyl isomerase (PPIase) inhibition to FK506 itself. The authors have also solved the structure of one of these ligands in complex with FKBP12, and have compared that structure to the FK506-FKBP12 complex. Consistent with the obsd. inhibitory equipotency of these compds., the authors observe a strong similarity in the conformation of the two ligands in the region of the protein that mediates PPIase activity. The compds., however, are not immunosuppressive. In the FKBP12-FK506 complex, a significant portion of the FK506 ligand, its 'effector domain', projects beyond the envelope of the binding protein in a manner that is suggestive of a potential interaction with a second protein, the calcium-dependent phosphatase, calcineurin, whose inhibition by the FKBP12-FK506 complex interrupts the T-cell activation events leading to immunosuppression. In contrast, the compds. bind within the surface envelope of FKBP12, and induce significant changes in the structure of the FKBP12 protein which may also affect calcineurin binding indirectly.
IT **145913-08-2**
RL: BPR (Biological process); PRP (Properties); BIOL (Biological study); PROC (Process)
(anal. of the interaction between FKBP12 and non-macrocyclic ligands in relation to the interaction between FKBP12 and the immunosuppressant FK506)

L17 ANSWER 15 OF 16 HCAPLUS COPYRIGHT 2000 ACS

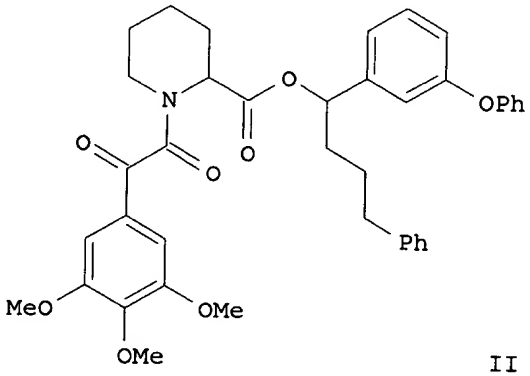
AN 1995:274880 HCAPLUS
DN 122:55896
TI 1-(2-oxoacetyl)piperidine-2-carboxylic acid derivatives as multi-drug-resistant cancer cell sensitizers
IN Armistead, David M.; Saunders, Jeffrey O.; Boger, Joshua S.
PA Vertex Pharmaceuticals Inc., USA
SO PCT Int. Appl., 111 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 4

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9407858	A1	19940414	WO 1993-US9145	19930927
	W: AT, AU, BB, BG, BR, BY, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, LV, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, UZ, VN				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	IL 107109	A1	19990312	IL 1993-107109	19930926
	EP 662958	A1	19950719	EP 1993-922748	19930927
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
	JP 08502256	T2	19960312	JP 1993-509216	19930927
	HU 72046	A2	19960328	HU 1995-890	19930927
	AU 690082	B2	19980423	AU 1993-51648	19930927
	CN 1088577	A	19940629	CN 1993-118201	19930928
	FI 9501454	A	19950327	FI 1995-1454	19950327
	NO 9501162	A	19950529	NO 1995-1162	19950327

PRAI US 1992-952299 19920928
WO 1993-US9145 19930927
OS MARPAT 122:55896
GI



I



II

AB The invention relates to compds. I [A = CH2, O, NH, alkylimino; B, D = (un)substituted (hetero)aryl, alk(en)(yn)yl, cycloalk(en)ylalk(en)(yn)yl, (hetero)aralkyl, cis-C(Q):CHT; Q = H, alk(en)(yn)yl; T = (un)substituted (hetero)aryl, substituted cycloalkyl; L = H, U; M = O, CHU; U = H, alk(en)yl, cycloalk(en)ylalk(en)yl, (hetero)aralk(en)yl, (hetero)aryl; J = H, alkyl, CH2Ph; K = alkyl, CH2Ph, cyclohexylmethyl; or JK = atoms to form 5- to 7-membered, optionally O- or S-contg. heterocycle; m = 0-3; various provisos], as well as pharmaceutical compns. comprising them. The compds. maintain, increase, or restore sensitivity of cells to therapeutic or prophylactic agents, and are particularly well-suited for treatment or prevention of multi-drug resistant cancer cells. Over 100 I are reported, including both single and mixed diastereomers. For example, 3-PhOC6H4CH2OH underwent oxidn. to the aldehyde and reaction with Ph(CH2)3MgBr to give the racemic alc. 3-PhOC6H4CH(OH)(CH2)3Ph. Esterification of this with (S)-N-[(3,4,5-trimethoxyphenyl)glyoxyl]pipecolic acid (prepn. given) yielded the ester II as a mixt. of diastereomers.

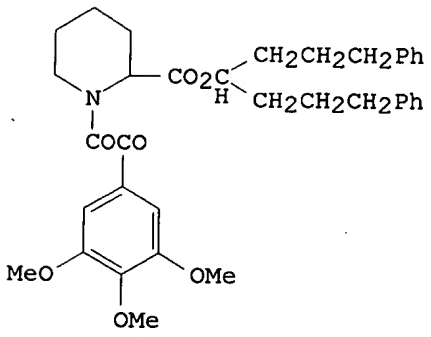
In a test for reversal of multi-drug-resistance by a line of L1210 cells, selected I gave up to 18-fold increase in the antiproliferative potency of doxorubicin.

IT **145912-99-8P 145913-00-4P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, as sensitizer for multi-drug-resistant cancer cells)

L17 ANSWER 16 OF 16 HCAPLUS COPYRIGHT 2000 ACS
AN 1993:495338 HCAPLUS
DN 119:95338
TI Preparation of 1-[(3,4,5-trimethoxyphenyl)glyoxyl]pipecolic esters as immunosuppressive compounds
IN Armistead, David M.
PA Vertex Pharmaceuticals Inc., USA
SO PCT Int. Appl., 67 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 4

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9219593	A1	19921112	WO 1992-US3913	19920511
	W: AT, AU, BB, BG, BR, CA, CH, CS, DE, DK, ES, FI, GB, HU, JP, KP, KR, LK, LU, MG, MN, MW, NL, NO, PL, RO, RU, SD, SE				
	RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GN, GR, IT, LU, MC, ML, MR, NL, SE, SN, TD, TG				
	CA 2102180	AA	19921110	CA 1992-2102180	19920511
	AU 9219957	A1	19921221	AU 1992-19957	19920511
	EP 584223	A1	19940302	EP 1992-912076	19920511
	EP 584223	B1	19990811		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
	JP 06508125	T2	19940914	JP 1992-512042	19920511
	HU 68332	A2	19950628	HU 1993-3184	19920511
	AT 183178	E	19990815	AT 1992-912076	19920511
PRAI	US 1991-697785	19910509			
	WO 1992-US3913	19920511			

OS MARPAT 119:95338
GI



II

AB LC(:M)CONJCHKCOA(CH2)nCHBD [I; A = O, NH, N-C1-4 alkyl; B, D = (substituted) Ph, -naphthyl, -mono-, -bicyclicheterocylyl; substituted C5-7 cycloalkyl, C5-7 cycloalkenyl; L = H, U wherein U = H, O-C1-4 alkyl, O-C1-4 alkenyl, C1-6 alkyl, C1-6 alkenyl, etc.; M = O, CHU; J = H, C1-2 alkyl, PhCH2; K = C1-4 alkyl, PhCH2, cyclohexylmethyl; JK = 5-7-membered heterocyclyl; n = 0-3], stereoisomers and salts thereof, are prepd. Ph(CH2)3CHO (prepn. given) was treated with Ph(CH2)3MgBr (prepn. given) to give the alc. which was condensed with (S)-BOC-pipecolic acid to give the ester which was deprotected and treated with 3,4,5-(MeO)3C6H2COCO2H to give the pipecolate (S)-II. In a test for immunosuppressive activity the Ki for inhibition of FK-506 binding protein rotamase activity II was 1.0

nM. Addnl. I were prepd. and tested.
IT **145913-08-2**
RL: RCT (Reactant)
(immunosuppressant)
IT **145912-99-8P 145913-00-4P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. and reaction of, in prepn. of immunosuppressants)

=> d his l18-

(FILE 'REGISTRY' ENTERED AT 16:21:44 ON 27 MAR 2000)

FILE 'HCAPLUS, USPATFULL' ENTERED AT 16:22:03 ON 27 MAR 2000

FILE 'BIOSIS' ENTERED AT 16:22:19 ON 27 MAR 2000
L18 4 S L7

FILE 'EMBASE' ENTERED AT 16:22:49 ON 27 MAR 2000
L19 5 S L7

FILE 'BIOSIS, EMBASE' ENTERED AT 16:23:03 ON 27 MAR 2000
L20 6 DUP REM L18 L19 (3 DUPLICATES REMOVED)

=> fil biosis embase

FILE 'BIOSIS' ENTERED AT 16:23:20 ON 27 MAR 2000
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FILE 'EMBASE' ENTERED AT 16:23:20 ON 27 MAR 2000
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=> d all tot l20

L20 ANSWER 1 OF 6 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
AN 2000069215 EMBASE
TI Immunophilin ligands as a novel treatment for neurological disorders.
AU Herdegen T.; Fischer G.; Gold B.G.
CS Prof. T. Herdegen, Institute of Pharmacology, University of Kiel, Hospitalstrasse 4, 24105 Kiel, Germany. t.herdegen@pharmakologie.uni-kiel.de
SO Trends in Pharmacological Sciences, (2000) 21/1 (3-5).
Refs: 9
ISSN: 0165-6147 CODEN: TPHSDY
PUI S 0165-6147(99)01407-8
CY United Kingdom
DT Journal; Conference Article
FS 008 Neurology and Neurosurgery
030 Pharmacology
037 Drug Literature Index
LA English
CT Medical Descriptors:
*neurologic disease: DT, drug therapy
*neurologic disease: ET, etiology
*neuroprotection
T lymphocyte
lymphocyte depletion
nerve regeneration
diabetes mellitus
diabetic neuropathy: CO, complication
diabetic neuropathy: DT, drug therapy
brain ischemia: DT, drug therapy
antiinflammatory activity
degenerative disease: DT, drug therapy

degenerative disease: ET, etiology
human
clinical trial
conference paper
priority journal
Drug Descriptors:
*immunophilin: EC, endogenous compound
*neuroprotective agent: DV, drug development
*neuroprotective agent: DT, drug therapy
*neuroprotective agent: PD, pharmacology
*tsukubaenolide: DT, drug therapy
*tsukubaenolide: PD, pharmacology
*fk 506 binding protein: DV, drug development
*fk 506 binding protein: PD, pharmacology
*1 (3,3 dimethyl 1,2 dioxopentyl) 2 pyrrolidinecarboxylic acid 3 (3 pyridyl)propyl ester: DV, drug development
*1 (3,3 dimethyl 1,2 dioxopentyl) 2 pyrrolidinecarboxylic acid 3 (3 pyridyl)propyl ester: PD, pharmacology
*timcodar: CT, clinical trial
*timcodar: DT, drug therapy
*timcodar: PD, pharmacology
ligand
calcineurin: EC, endogenous compound
calcium ion: EC, endogenous compound
*fk 506 binding protein: EC, endogenous compound
epidermal growth factor receptor: EC, endogenous compound
collagen: EC, endogenous compound
cis trans isomerase: EC, endogenous compound
ryanodine receptor: EC, endogenous compound
caffeine
adenine
vx 853: CT, clinical trial
vx 853: DT, drug therapy
vx 853: PD, pharmacology
heat shock protein 90: EC, endogenous compound
cyclosporin A

RN (tsukubaenolide) 104987-11-3; (calcineurin) 137951-12-3; (calcium ion) 14127-61-8; (collagen) 9007-34-5; (caffeine) 30388-07-9, 58-08-2; (adenine) 22177-51-1, 2922-28-3, 73-24-5; (cyclosporin A) 59865-13-3, 63798-73-2

CN Fk 506; **V 10367**; Gpi 1046; Vx 853

L20 ANSWER 2 OF 6 BIOSIS COPYRIGHT 2000 BIOSIS

AN 2000:67336 BIOSIS

DN PREV200000067336

TI Neurophilin ligands: Protective and trophic effects in animal models of Parkinson's disease.

AU Costantini, L. C. (1); Cole, D.; Chaturvedi, P.; Isacson, O. (1)

CS (1) Neuroregeneration Laboratory, McLean Hospital, Harvard Medical School, Belmont, MA USA

SO Society for Neuroscience Abstracts, (1999) Vol. 25, No. 1-2, pp. 293. Meeting Info.: 29th Annual Meeting of the Society for Neuroscience, Part 1 Miami Beach, Florida, USA October 23-28, 1999 The Society for Neuroscience . ISSN: 0190-5295.

DT Conference

LA English

CC Nervous System - General; Methods *20501
Endocrine System - General *17002
Pharmacology - General *22002
General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals *00520

BC Muridae 86375

IT Major Concepts
Nervous System (Neural Coordination); Pharmacology

IT Parts, Structures, & Systems of Organisms
striatum: nervous system

IT Diseases
Parkinson's disease: nervous system disease
IT Chemicals & Biochemicals
V-10,367: antiparkinsonian - drug, neurophilin ligand; V-13,661: antiparkinsonian - drug, neurophilin ligand; dopamine
IT Alternate Indexing
Parkinson Disease (MeSH)
IT Miscellaneous Descriptors
Meeting Abstract
ORGN Super Taxa
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
mouse (Muridae): animal model
ORGN Organism Superterms
Animals; Chordates; Mammals; Nonhuman Mammals; Nonhuman Vertebrates; Rodents; Vertebrates
RN 51-61-6 (DOPAMINE)

L20 ANSWER 3 OF 6 BIOSIS COPYRIGHT 2000 BIOSIS DUPLICATE 1
AN 1999:106384 BIOSIS
DN PREV199900106384
TI Tacrolimus (FK506) increases neuronal expression of GAP-43 and improves functional recovery after spinal cord injury in rats.
AU Madsen, Joseph R. (1); MacDonald, Paul; Irwin, Nina; Goldberg, David E.; Yao, Gui-Lan; Meiri, Karina F.; Rimm, Ilonna J.; Stieg, Philip E.; Benowitz, Larry I.
CS (1) Dep. Neurosurgery, Child. Hosp., 300 Longwood Avenue, Boston, MA 02115 USA
SO Experimental Neurology, (Dec., 1998) Vol. 154, No. 2, pp. 673-683. ISSN: 0014-4886.
DT Article
LA English
AB Tacrolimus (FK506), a widely used immunosuppressant drug, has neurite-promoting activity in cultured PC12 cells and peripheral neurons. The present study investigated whether tacrolimus affects the expression of the neuronal growth-associated protein, GAP43, as well as functional recovery after photothrombotic spinal cord injury in the rat. In injured animals receiving tacrolimus, the number of neurons expressing GAP-43 mRNA and protein approximately doubled compared to that in injured animals receiving vehicle alone. This increase in GAP-43-positive cells was paralleled by a significant improvement in neurological function evaluated by open-field and inclined plane tests. Another FKBP-12 ligand (**V -10,367**) had similar effects on GAP-43 expression and functional outcome, indicating that the observed effects of tacrolimus do not involve inhibition of the phosphatase calcineurin. Thus, tacrolimus, a drug which is already approved for use in humans, as well as other FKBP-12 ligands which do not inhibit calcineurin, could potentially enhance functional outcome after CNS injury in humans.
CC Pharmacology - General *22002
Biochemical Studies - General *10060
Nervous System - General; Methods *20501
BC Muridae 86375
IT Major Concepts
Nervous System (Neural Coordination); Pharmacology
IT Parts, Structures, & Systems of Organisms
neurons: nervous system; spinal cord: nervous system; CNS [central nervous system]: nervous system
IT Chemicals & Biochemicals
calcineurin; mRNA [messenger RNA]: expression; tacrolimus [FK506]: immunosuppressant - drug; GAP-43: expression
ORGN Super Taxa
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
rat (Muridae)
ORGN Organism Superterms

Animals; Chordates; Mammals; Nonhuman Mammals; Nonhuman Vertebrates; Rodents; Vertebrates
RN 104987-11-3 (TACROLIMUS)
104987-11-3 (FK506)
9025-75-6 (CALCINEURIN)

L20 ANSWER 4 OF 6 BIOSIS COPYRIGHT 2000 BIOSIS DUPLICATE 2
AN 1998:169385 BIOSIS
DN PREV199800169385
TI Oral administration of a nonimmunosuppressant FKBP-12 ligand speeds nerve regeneration.
AU Gold, Bruce G. (1); Zeleny-Pooley, Michelle; Chaturvedi, Pravin; Wang, Min-Sheng
CS (1) Cent. Res. Occup. Environ. Tolxicol./L606, Oregon Health Sci. Univ., 3181 SW Sam Jackson Park Road, Portland, OR 97201-3098 USA
SO Neuroreport, (Feb. 16, 1998) Vol. 9, No. 3, pp. 553-558.
ISSN: 0959-4965.
DT Article
LA English
AB We recently showed that s.c. injections of a nonimmunosuppressant FK506 binding protein-12 (FKBP-12) ligand (**V-10,367**) accelerates nerve regeneration in the rat sciatic nerve crush model. Here we examined the oral efficacy of this compound for speeding nerve regeneration. Rats receiving **V- 10,367** (5, 15 or 50 mg/kg/day) by oral gavage all demonstrated an increase in nerve regeneration compared to vehicle-treated controls. Functional recovery was observed earliest and axonal calibers of regenerating axons in the soleus nerve were largest in the 15 mg/kg group, mean axonal areas being increased by 66% compared to controls. Orally active nonimmunosuppressant FKBP-12 ligands may be useful for the treatment of human peripheral nerve disorders.
CC Nervous System - Pathology *20506
Biochemical Studies - General *10060
Biochemical Studies - Proteins, Peptides and Amino Acids *10064
BC Muridae 86375
IT Major Concepts
Nervous System (Neural Coordination)
IT Parts, Structures, & Systems of Organisms
nerve: regeneration, nervous system
IT Diseases
peripheral nerve disorder: nervous system disease
IT Chemicals & Biochemicals
FK506 binding protein-12: oral administration, nonimmunosuppressant
ORGN Super Taxa
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
Sprague-Dawley rat (Muridae): animal model
ORGN Organism Superterms
Animals; Chordates; Mammals; Nonhuman Mammals; Nonhuman Vertebrates; Rodents; Vertebrates

L20 ANSWER 5 OF 6 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
AN 1998316403 EMBASE
TI A novel immunophilin ligand: Distinct branching effects on dopaminergic neurons in culture and neurotrophic actions after oral administration in an animal model of Parkinson's disease.
AU Costantini L.C.; Chaturvedi P.; Armistead D.M.; McCaffrey P.G.; Deacon T.W.; Isacson O.
CS L.C. Costantini, Neuroregeneration Laboratory, Harvard Medical School, McLean Hospital, 115 Mill Street, Belmont, MA 02178, United States. Costanti@helix.mgh.harvard.edu
SO Neurobiology of Disease, (1998) 5/2 (97-106).
Refs: 52
ISSN: 0969-9961 CODEN: NUDIEM
CY United States
DT Journal; Article

FS 008 Neurology and Neurosurgery
026 Immunology, Serology and Transplantation
037 Drug Literature Index
LA English
SL English
AB Protection or regeneration of the dopaminergic (DA) system would be of significant therapeutic value for Parkinson's disease. Immunophilin ligands, such as FK506, can produce neurotrophic effects in vitro and in vivo, but their immunosuppressive effects make them unsuitable for neurological application. This study demonstrates that a novel, nonimmunosuppressive immunophilin ligand (**V-10, 367**) increased the number of neurites extended by tyrosine hydroxylase positive (TH+) DA neurons in embryonic day 14 primary DA neuronal cultures. In contrast, the immunosuppressive immunophilin ligand FK506 increased the length of TH+ neurites. After oral administration in MPTP-treated mice, **V-10,367** completely protected against MPTP-induced loss of striatal TH+ axonal density, while FK506 did not. These experiments demonstrate that nonimmunosuppressive immunophilin ligands specifically increase neurite branching in primary DA neuronal cultures and possess neurotrophic actions in vivo with potential application to neurodegenerative disease.
CT Medical Descriptors:
*parkinson disease: ET, etiology
*parkinson disease: PC, prevention
*brain protection
*dopaminergic nerve cell
neurologic disease: ET, etiology
neurologic disease: PC, prevention
degenerative disease: ET, etiology
degenerative disease: PC, prevention
experimental model
nerve cell culture
dopaminergic system
nonhuman
mouse
animal model
controlled study
animal cell
embryo
oral drug administration
article
priority journal
Drug Descriptors:
*immunophilin
*ligand
*fk 506 binding protein: AD, drug administration
*fk 506 binding protein: CM, drug comparison
*fk 506 binding protein: PD, pharmacology
*tsukubaenolide: AD, drug administration
*tsukubaenolide: CM, drug comparison
*tsukubaenolide: PD, pharmacology
*immunosuppressive agent: AD, drug administration
*immunosuppressive agent: CM, drug comparison
*immunosuppressive agent: PD, pharmacology
1,2,3,6 tetrahydro 1 methyl 4 phenylpyridine
RN (tsukubaenolide) 104987-11-3; (1,2,3,6 tetrahydro 1 methyl 4 phenylpyridine) 28289-54-5
CN **V 10367**; Fk 506

L20 ANSWER 6 OF 6 BIOSIS COPYRIGHT 2000 BIOSIS DUPLICATE 3
AN 1997:519444 BIOSIS
DN PREV199799818647
TI A non-immunosuppressant FKBP-12 ligand increases nerve regeneration.
AU Gold, Bruce G. (1); Zeleny-Pooley, Michelle (1); Wang, Min-Sheng (1); Chaturvedi, Pravin; Armistead, David M.
CS (1) Cent. Res. Occupational Environmental Toxicol., Oregon Health Sci.

Univ., Portland, OR 97201-3098 USA

SO Experimental Neurology, (1997) Vol. 147, No. 2, pp. 269-278.
ISSN: 0014-4886.
DT Article
LA English

AB The immunosuppressant drugs FK506 and cyclosporin A inhibit T-cell proliferation via a common mechanism: calcineurin inhibition following binding to their respective binding proteins, the peptidyl prolyl isomerases FKBP-12 and cyclophilin A. In contrast, FK506, but not cyclosporin A, accelerates nerve regeneration. In the present study, we show that the potent FKBP-12 inhibitor **V-10, 367**, which lacks the structure components of FK506 required for calcineurin inhibition, increases neurite outgrowth in SH-SY5Y neuroblastoma cells and speeds nerve regeneration in the rat sciatic nerve crush model. In SH-SY5Y cells, **V-10,367** increased the lengths of neurite processes in a concentration-dependent (between 1 and 10 nM) fashion over time (up to 168 h). Daily subcutaneous injections of **V-10,367** accelerated the onset of clinical signs of functional recovery in the hind feet compared to vehicle-treated control animals. Interdigit distances (between the first and fifth digits) measured on foot prints obtained during walking showed an increase in toe spread in **V-10,367**-treated rats compared to vehicle-treated controls. Electron microscopy demonstrated larger regenerating axons distal to the crush site in the sciatic nerve from **V-10,367**-treated rats. Quantitation of axonal areas in the soleus nerve revealed a shift to larger axonal calibers in **V-10,367**-treated rats (400 or 200 mg/kg/day); mean axonal areas were increased by 52 and 59%, respectively, compared to vehicle-treated controls. FKBP-12 ligands lacking calcineurin inhibitory activity represent a new class of potential drugs for the treatment of human peripheral nerve disorders.

CC Biochemical Studies - General *10060
Nervous System - General; Methods *20501
Pharmacology - General *22002
Immunology and Immunochemistry - General; Methods *34502
BC Hominidae 86215
Muridae *86375
IT Major Concepts
Biochemistry and Molecular Biophysics; Immune System (Chemical Coordination and Homeostasis); Nervous System (Neural Coordination); Pharmacology
IT Chemicals & Biochemicals
FK506; CYCLOSPORIN A
IT Miscellaneous Descriptors
CALCINEURIN; CYCLOSPORIN A; FKBP-12; FKBP-12 INHIBITOR; FK506; IMMUNOSUPPRESSANT-DRUG; INHIBITION; NERVE REGENERATION; NERVOUS SYSTEM; NON-IMMUNOSUPPRESSANT LIGAND; PHARMACOLOGY; **V-10, 367**
ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia; Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
rat (Muridae); SH-SY5Y (Hominidae): cell line
ORGN Organism Superterms
animals; chordates; humans; mammals; nonhuman mammals; nonhuman vertebrates; primates; rodents; vertebrates
RN 104987-11-3 (FK506)
59865-13-3 (CYCLOSPORIN A)

L7 ANSWER 5 OF 5 CAPLUS COPYRIGHT 2000 ACS
AN 1997:224774 CAPLUS
DN 126:312111
TI Neurotrophic actions of **non-immunosuppressive** analogs of immunosuppressive drugs FK506, rapamycin and cyclosporin A
AU Steiner, Joseph P.; Connolly, Maureen A.; Valentine, heather L.; Hamilton, Gregory S.; Dawson, Ted M.; Hester, Lynda; Snyder, Solomon H.
CS Dep. Neurobiol. Res., Guilford Pharm. Inc., Baltimore, MD, 21224, USA
SO Nat. Med. (N. Y.) (1997), 3(4), 421-428
CODEN: NAMEFI; ISSN: 1078-8956
PB Nature Publishing Co.
DT Journal
LA English
AB We show that the **non-immunosuppressive** analogs of the immunosuppressive drugs FK506, rapamycin and cyclosporin A promote neurite outgrowth both in PC12 cells and sensory neuronal cultures of dorsal root ganglia with potencies resembling their immunosuppressive homologues. Neurotrophic potencies of the **immunophilin ligands** resemble their potencies in binding to and inhibiting the rotamase activity of FKBP-12 or cyclophilin. Since nonimmunosuppressive **immunophilin ligands**, which are devoid of calcineurin inhibitory activity, are equally neurotrophic, inhibition of calcineurin activity is not the mediator of the neurotrophic effects. The **immunophilin ligands** are neurotrophic in intact animals. FK506 and L-685,818 (the C18-hydroxy, C21-Et deriv. of FK506) treatment of rats with crushed sciatic nerves enhances both functional and morphol. recovery. The striking potency of these agents, their bioavailability and the dissocn. of neurotrophic from immunosuppressant actions argue for their therapeutic relevance in the treatment of neurodegenerative disease

L7 ANSWER 4 OF 5 CAPLUS COPYRIGHT 2000 ACS
AN 1997:173890 CAPLUS
DN 126:272710
TI Neurotrophic **immunophilin ligands** stimulate structural and functional recovery in neurodegenerative animal models
AU Steiner, Joseph P.; Hamilton, Gregory S.; Ross, Douglas T.; Valentine, Heather L.; Guo, Hongzhi; Connolly, Maureen A.; Liang, Shi; Ramsey, Cynthia; Li, Jia-He J.; Huang, Wei; Howorth, Pamela; Soni, Rajat; Fuller, Michael; Sauer, Hans; Nowotnik, Alison c.; Suzdak, Peter D.
CS Deps. Neurobiol. Res. Med. Chem., Guilford Pharmaceuticals Inc., Baltimore, MD, 21224, USA
SO Proc. Natl. Acad. Sci. U. S. A. (1997), 94(5), 2019-2024
CODEN: PNASA6; ISSN: 0027-8424
PB National Academy of Sciences
DT Journal
LA English
AB Although immunosuppressant **immunophilin ligands** promote neurite outgrowth in vitro, their neurotrophic activities are clearly independent of their immuno-suppressive activity. In the present report, a novel **non-immunosuppressive immunophilin ligand**, GPI-1046 (I) is described. In vitro, GPI-1046 bound to FK506-binding protein-12 and elicited neurite outgrowth from sensory neuronal cultures with picomolar potency with maximal effects comparable to nerve growth factor. In vivo, GPI-1046 stimulated the regeneration of lesioned sciatic nerve axons and myelin levels. In the central nervous system, GPI-1046 promoted protection and/or sprouting of serotonin-contg. nerve fibers in somatosensory cortex following parachloramphetamine treatment. GPI-1046 also induced regenerative sprouting from spared nigrostriatal dopaminergic neurons following 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine toxicity in mice or 6-hydroxydopamine (6-OHDA) toxicity in rats. The rotational abnormality in 6-OHDA-treated rats was alleviated by GPI-1046. These neurotrophic actions in multiple models suggest therapeutic utility for GPI-1046 in neurode

L7 ANSWER 3 OF 5 MEDLINE
AN 1998170649 MEDLINE
DN 98170649
TI Neural actions of **immunophilin ligands**.
AU Snyder S H; Sabatini D M; Lai M M; Steiner J P; Hamilton G S; Suzdak P D
CS Department of Neuroscience, Johns Hopkins University School of Medicine, Baltimore, MD 21205, USA.
NC MH-18501 (NIMH)
DA-00266 (NIDA)
DA-00074 (NIDA)
+
SO TRENDS IN PHARMACOLOGICAL SCIENCES, (1998 Jan) 19 (1) 21-6. Ref: 42
Journal code: WFT. ISSN: 0165-6147.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
EM 199806
EW 19980601
AB Immunophilins, protein receptors for immunosuppressant drugs such as cyclosporin A and FK506, are enriched far more in the brain than in the immune system. Drug-immunophilin complexes bind to calcineurin, inhibiting its phosphatase activity and leading to immunosuppressant effects. The immunophilin FKBP-12 (FK506 binding protein, 12 kDa) forms a complex with the ryanodine and inositol (1,4,5) trisphosphate (IP3) receptors to regulate their physiological release of intracellular Ca2+. Here, Solomon Snyder and colleagues describe how **non-immunosuppressant** as well as immunosuppressant **immunophilin ligands** are neurotrophic for numerous classes of damaged neurones, both in culture systems and intact animals. Their ability to stimulate functional regrowth of damaged sciatic, cortical cholinergic, dopamine and 5-HT neurones may h

TI The **immunophilin ligand** FK506, but not GPI-1046, protects against neuronal death and inhibits c-Jun expression in the substantia nigra pars compacta following transection of the rat medial forebrain bundle

AU Winter, C.; Schenkel, J.; Burger, E.; Eickmeier, C.; Zimmermann, M.; Herdegen, T.

CS II Institute of Physiology, University of Heidelberg, Heidelberg, 69120, Germany

SO Neuroscience (Oxford) (1999), Volume Date 2000, 95(3), 753-762
CODEN: NRSCDN; ISSN: 0306-4522

PB Elsevier Science Ltd.

DT Journal

LA English

AB The **immunophilin ligand** FK506 (Tacrolimus) is used for prevention of graft rejection following organ transplantation. FK506 is a high-affinity ligand for FK506-binding proteins, an immunophilin subgroup of peptidyl-prolyl-cis/trans-rotamases abundant in the mammalian brain. Here, we demonstrate that FK506 is a potent survival factor that prevents neuronal cell death following axotomy of central intrinsic neurons. Administration of FK506 (2 mg/kg, s.c., per day for two days pre-axotomy and for up to eight days post-axotomy) effectively delayed and reduced the death of axotomized neurons in the substantia nigra pars compacta following transection of the medial forebrain bundle. In saline-treated controls, 75%, 89% and 92% of nigral neurons died after 25, 50 and 60 days post-axotomy, resp. In contrast, application of FK506 resulted in survival of 46%, 44% and 28% of the axotomized nigral neurons, and the majority of these surviving neurons showed continuous expression of tyrosine hydroxylase, the pacemaker enzyme for dopamine synthesis. Moreover, FK506 significantly reduced the expression of the inducible transcription factor c-Jun and its N-terminal phosphorylation and prevented the axotomy-induced suppression of the constitutive transcription factor ATF-2 in neurons of the substantia nigra and mammillary body. The latter is also axotomized by the coincident transection of the mammillothalamic tract, but the mammillary neurons survive the axotomy. In contradistinction to FK506, the **non-immunosuppressive** FK506-binding protein ligand GPI-1046 (25 or 12.5 mg/kg, applied once or twice per day for two days pre-axotomy and for eight days post-axotomy) was completely ineffective for all these parameters investigated. Finally, FK506, but not GPI-1046, impressively accelerated the recovery from surgery. Our data provide the first evidence that FK506 acts as a neuroprotective mol. that rescues axotomized otherwise degenerating central intrinsic neurons in the adult mammalian brain by mechanisms that interfere with the transcriptional program of the axotomy-induced cell body response, such as activating transcription factor-2 suppression and c-Jun expression and phosphorylation.

L7 ANSWER 1 OF 5 MEDLINE
AN 2000133902 MEDLINE
DN 20133902
TI The **immunophilin ligand** FK506, but not GPI-1046, protects against neuronal death and inhibits c-Jun expression in the substantia nigra pars compacta following transection of the rat medial forebrain bundle.
AU Winter C; Schenkel J; Burger E; Eickmeier C; Zimmermann M; Herdegen T
CS II Institute of Physiology, University of Heidelberg, Germany.
SO NEUROSCIENCE, (2000) 95 (3) 753-62.
Journal code: NZR. ISSN: 0306-4522.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200005
EW 20000501
AB The **immunophilin ligand** FK506 (Tacrolimus) is used for prevention of graft rejection following organ transplantation. FK506 is a high-affinity ligand for FK506-binding proteins, an immunophilin subgroup of peptidyl-prolyl-cis/trans-rotamases abundant in the mammalian brain. Here, we demonstrate that FK506 is a potent survival factor that prevents neuronal cell death following axotomy of central intrinsic neurons. Administration of FK506 (2 mg/kg, s.c., per day for two days pre-axotomy and for up to eight days post-axotomy) effectively delayed and reduced the death of axotomized neurons in the substantia nigra pars compacta following transection of the medial forebrain bundle. In saline-treated controls, 75%, 89% and 92% of nigral neurons died after 25, 50 and 60 days post-axotomy, respectively. In contrast, application of FK506 resulted in survival of 46%, 44% and 28% of the axotomized nigral neurons, and the majority of these surviving neurons showed continuous expression of tyrosine hydroxylase, the pacemaker enzyme for dopamine synthesis. Moreover, FK506 significantly reduced the expression of the inducible transcription factor c-Jun and its N-terminal phosphorylation and prevented the axotomy-induced suppression of the constitutive transcription factor ATF-2 in neurons of the substantia nigra and mammillary body. The latter is also axotomized by the coincident transection of the mammillothalamic tract, but the mammillary neurons survive the axotomy. In contradistinction to FK506, the **non-immunosuppressive** FK506-binding protein ligand GPI-1046 (25 or 12.5 mg/kg, applied once or twice per day for two days pre-axotomy and for eight days post-axotomy) was completely ineffective for all these parameters investigated. Finally, FK506, but not GPI-1046, impressively accelerated the recovery from surgery. Our data provide the first evidence that FK506 acts as a neuroprotective molecule that rescues axotomized otherwise degenerating central intrinsic neurons in the adult mammalian brain by mechanisms that interfere with the transcriptional program of the axotomy-induced cell body response, such as activating transcription factor-2 suppression and c-Jun expression and phosphorylation.